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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/552,839	11/03/95	WANG	0	CELL-16.3

EXAMINER	
GUZO, D	
ART UNIT	**PAPER NUMBER**
1636	6

HM11/0218

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DATE MAILED: 02/18/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 11/7/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire Three (3) month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 37-61 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 37-61 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892 (2)
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

SEE OFFICE ACTION ON THE FOLLOWING PAGES

1. Applicant's election of Group I (Claims 37-61) in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The disclosure is objected to because of the following informalities: Numerous ATCC accession numbers are missing form the specification, i.e. see pages 6, 8, 15, etc. If applicants attempt to add ATCC Accession numbers by amendment, applicants are cautioned against the addition of new matter.

Appropriate correction is required.

Claims reading on the adenoviral E2A gene, cell lines containing said gene and adenoviral vectors deficient in said gene are first described in the instant application, and therefore priority for these embodiments is granted back to 11/3/95.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Klessig et al. or Brough et al.

Applicants claim a DNA plasmid comprising an adenoviral E2A gene operably linked to an

inducible promoter.

Klessig et al. (Mol. Cell. Biol., Vol. 4, No. 7, July 1984, pp. 1354-1362, see whole article, particularly Fig. 1) and Brough et al. (Virology, Vol. 190, 1992, pp. 624-634, see whole article, particularly p. 625 and Fig. 1) both recite a DNA plasmid comprising an adenoviral E2A gene (which encodes the adenovirus ssDNA binding protein (DBP)) operably linked to the inducible MMTV promoter. Therefore, Klessig et al. and Brough et al. teach the claimed invention.

4. Claims 49, 50 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Weinberg et al.

Applicants recite packaging cell lines that support growth of replication defective adenoviruses or recombinant adenoviral vectors wherein said viruses or vectors comprise mutations or deletions of any kind in the E1, E2A or E4-ORF6 regions and optionally a deletion of the E3 gene region.

Weinberg et al. (PNAS, Vol. 80, September 1983, pp. 5383-5386, see whole article, particularly p. 5383 and 5386) recites cells (i.e. 293 or W162 cells) capable of supporting growth of recombinant adenoviral vectors or mutant viruses wherein the viruses have deletions in E1 or E4. It is noted that since applicants' claims do not specify the nature of the mutations or deletions in the recited adenoviral genes, said deletions or mutations can read on silent mutations or deletions which do not affect the activity of the gene products encoded by the recited adenoviral genes. Therefore, Weinberg et al. teaches the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 55 and 56 are rejected under 35 U.S.C. 102(a) as being anticipated by Armentano et al.

Applicants claim recombinant adenoviral vectors comprising deletions in the E1, E4 and optionally the E3 regions and a transgene replacing any of said deletions.

Armentano et al. (J. Cell. Biochem., Supplement 18 Part A, January 15-22, 1994, see whole article) recites a recombinant adenoviral vector for expressing a foreign gene of interest, said vector comprising deletions in the adenoviral E1, E4 and E3 gene regions. Therefore, Armentano et al. teaches the claimed invention.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 44-46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brough et al. or Klessig et al., either in view of Jyan-Gwo et al.

Brough et al. and Klessig et al. recite the expression of the E2A gene product (the adenovirus ssDNA binding protein, DBP) wherein E2A gene expression is controlled by the inducible MMTV promoter. Neither Brough et al. nor Klessig et al. recite the use of cAMP response element binding protein regulated genes such as murine alpha-inhibin.

Jyan-Gwo et al. recites a plasmid comprising a luciferase reporter gene linked to a promoter from a murine alpha-inhibin gene, and teach the promoter is induced to stimulate expression of the linked reporter gene in a cell that is treated with forskolin, an adenyl cyclase activator (pp. 288-289).

Expression of the E2A gene product is toxic to cells and hence expression must be regulated by inducible promoters. The prior art teaches use of the MMTV inducible promoter; however, no special feature of the MMTV inducible promoter appears to be required for expression of the E2A gene product and therefore it must be considered that any inducible promoter could be substituted for the MMTV promoter. Given that the alpha-inhibin promoter is well characterized, it must be considered that substitution of the alpha-inhibin promoter for the MMTV promoter would have been, absent unexpected results, a matter of design choice in vector design. The

ordinary skilled artisan, seeking to identify DBP mutants and cell lines capable of inducibly expressing the DBP protein, would have been motivated to induce the expression of the toxic DBP protein by using an inducible promoter such as the alpha-inhibin promoter because this inducible promoter system is well characterized (see Jyan-Gwo et al.) and could substitute for the MMTV promoter used by Brough et al. or Klessig et al. It would have been obvious for the ordinary skilled artisan to do this because an inducible promoter is necessary for expression of the toxic E2A protein product and the murine alpha-inhibin inducible promoter system is one of the best characterized inducible promoter systems. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that, absent evidence to the contrary, the claimed invention was prima facie obvious.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brough et al. or Klessig et al. either in view of Gossen et al.

Brough et al. and Klessig et al are cited as in the above 103 rejection of Claims 44-46 and 48.

Gossen et al. recites the tetracycline inducible promoter system.

The ordinary skilled artisan, seeking to characterize DBP mutants or cell lines capable of expressing this toxic protein, would have been motivated to express the protein using an inducible promoter system (as described by Klessig et al. and Brough et al.). Since the DBP protein is toxic to cells, a tightly regulated inducible promoter such as the tetracycline inducible promoter system as described by Gossen et al. would have been recognized as ideal by the ordinary skilled artisan since expression in the absence of tetracycline is very low. It would have been obvious for the

ordinary skilled artisan to substitute the tetracycline promoter for the MMTV promoter recited by Brough et al. and Klessig et al. because the well characterized tetracycline promoter is recited by Gossen et al. as being ideal for regulation of gene expression in eukaryotic cells (p. 5551).

7. Claims 37-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ketner et al. In view of Jyan-Gwo et al.

Ketner et al. disclose plasmids comprising a promoter operably linked to a DNA molecule comprising one or more of the open reading frames (ORFs) of the adenoviral E4 early region, and a method wherein the plasmid is transiently transfected into cultured mammalian cells so that the protein(s) encoded by the E4 region ORFs are produced in the cells, in order to identify E4 ORFs which are essential for adenoviral replication (pp. 3038-3045). Ketner et al. do not disclose plasmids wherein the promoter linked to the DNA comprising adenoviral E4 early region ORFs is an inducible promoter such as a promoter from a murine alpha-inhibin gene, which comprises a cAMP response element (CRE) and is induced by an agent which increases cellular cAMP concentration.

Jyan-Gwo et al. disclose a plasmid comprising a luciferase reporter gene linked to a promoter from a murine alpha-inhibin gene, and teach the promoter is induced to stimulate expression of the linked reporter gene in a cell that is treated with forskolin, an adenyl cyclase activator (pp. 288-289).

At the time the application was filed, it would have been obvious to one of ordinary skill in the art to follow the teachings of Ketner et al. to make plasmids comprising a promoter operably

linked to a DNA molecule comprising ORFs of the adenoviral E4 early region, for use in identifying the ORFs required for adenoviral replication, as discussed above, and to make instead plasmids comprising a promoter from a murine alpha-inhibin gene for stimulated expression in cells treated with an activator of adenyl cyclase as taught by Jyan-Gwo et al. as discussed above, given the recognition by those of ordinary skill in the art that plasmids comprising a promoter from a murine alpha-inhibin gene would reasonably have been expected to function successfully in forskolin-treated cells to direct expression of the E4 region ORFs in the same effective manner shown for the plasmids comprising non-inducible promoters as taught by Ketner et al. as discussed above, and given the recognition by those of ordinary skill in the art that choice of promoter used to obtain expression of the E4 ORFs for identification of ORFs required for adenoviral replication, would have been optimization of process parameters. Thus the invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

8. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ketner et al. In view of Jyan-Gwo et al. as applied to claims 37-40 and 42 above, and further in view of Gossen et al.

Ketner et al. in view of Jyan-Gwo et al. teach making a plasmid comprising an inducible promoter operably linked to a DNA molecule comprising one or more ORFs of the adenoviral E4 early region, for use in identifying the ORFs required for adenoviral replication, as discussed above; however, they do not teach making such a plasmid wherein the promoter is a tetracycline-responsive promoter.

Gossen et al. disclose a plasmid comprising a tetracycline-inducible promoter operably linked to a luciferase reporter gene, and show that the promoter is induced by tetracycline to give high levels of expression of the linked gene in mammalian cells which are co-transformed to produce a tetracycline-responsive transactivator protein (pp. 5547-5550).

At the time the invention was made, it would have been obvious to one or ordinary skill in the art to follow the teachings of Ketner et al. in view of Jyan-Gwo et al. to make a plasmid comprising an inducible promoter operably linked to a DNA molecule comprising one or more ORFs of the adenoviral E4 early region, for use in identifying the ORFs required for adenoviral replication, as discussed above, and to modify those teachings by making a plasmid comprising a tetracycline-inducible promoter operably linked to the E4 region ORFs, to obtain high, tetracycline-induced levels of expression of the linked adenoviral genes in cultured mammalian cells as taught by Gossen et al., given the recognition by those of ordinary skill in the art that a plasmid comprising such a tetracycline-inducible promoter would reasonably have been expected to function successfully in tetracycline treated cells comprising said tetracycline-responsive transactivator protein to direct expression of the E4 region ORFs in the same effective manner shown for the plasmids comprising non-inducible or forskolin inducible promoters as taught by Ketner et al. in view of Jyan-Gwo et al., as discussed above, and given the recognition by those of ordinary skill in the art that choice of promoter used to obtain expression of the E4 ORFs for identification of ORFs required for adenoviral replication, would have been optimization of process parameters. Thus the invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 53 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim plasmid constructs comprising adenoviral late genes under control of the tetracycline responsive promoter. However, nowhere in the instant specification do applicants disclose operably linking adenoviral late genes to the tetracycline inducible promoter, generating cell lines which could stably maintain said constructs, isolating the range of adenoviral genes involved and linking them to tetracycline inducible promoters, etc. It would appear that applicants' specification represents an invitation for the skilled artisan to experiment in order to try to isolate any or all of the adenoviral late genes, operably link them to the tetracycline responsive promoter (applicants provide no guidance on any specific constructs), and try to introduce them into cells which would allow for the expression of the late gene products (this last point is of particular importance since the claimed constructs would appear to have no disclosed use in the absence of a host cell line(s) which could maintain said constructs. Given the absence of guidance provided by applicants on the generation and use of said constructs, it must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to enable the claimed invention.

11. Claims 49-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 293 packaging cell lines capable of supporting growth of the claimed mutant adenoviral vectors, does not reasonably provide enablement for any packaging cell line that supports the growth of the claimed mutant adenovirus vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' specification only discloses 293 derived adenoviral packaging cell lines and provides no guidance as to how the skilled artisan would develop any other cell lines with the capacity to support growth of the recited adenoviral vectors. Since, at the time the instant invention was made, it was unclear what characteristics of the 293 cells were critical with regard to their being capable of stably maintaining and tolerating the presence of multiple adenoviral genes (i.e. the E1, E2A, E4 genes, etc.), it is unclear how the skilled artisan would even being to develop additional packaging cell lines with the claimed characteristics. Indeed, applicants specification does not even offer the skilled artisan an invitation to experiment since no criteria are given on how the skilled artisan would choose other cell lines as starting materials and manipulate them to stably maintain and inducible express the recited adenoviral genes as well as support the growth of the recited replication defective adenoviral vectors. The skilled artisan, attempting to practice the full scope of the claimed invention, would need to resort to trial and error experimentation, with no guidance from applicants. Said experimentation is the antithesis of enablement under 35 USC 112, 1st paragraph and said experimentation must be considered to be undue and excessive.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-42, 44-52 and 55-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 61 is vague in that it refers to canceled claims 21, 22 or 36.

Claims 42, 48 and 51 are vague in that ATCC or CRL numbers are missing.

Claims 38, 39, 44 and 45 are vague in their recitation of "the cAMP response element", "the gene encoding...mammalian alpha inhibin", etc. because the use of the definite article "the" incorrectly suggests that there is only one of each type of the recited elements.

Claim 49 is vague in that applicants recite deletions or mutations selected from groups of genes. A mutation or deletion is not a gene; possibly applicants mean to claim deletions or mutations **in genes** selected from the recited group of adenoviral genes.

Claims 49, 50, 52, 55-60 are vague in that applicants use language such as (in claim 50) "...comprises two deletions from the E1 and E4-ORF6 early gene regions..." or (in claim 57) "...comprises three deletions from the E1, E2A and E4 early gene regions...", etc. It is unclear if applicants mean, in claim 50 for example, to recite two deletions in each of the E1 and E4-ORF6 gene regions or one deletion in each of said genes.

No Claims are allowed.

Certain papers related to this application may be submitted to ART Unit 1636 via facsimile transmission. The FAX Number for this Art Unit is (703) 308-4242 or (703) 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (Nov. 16, 1993) and 1157 OG 94 (Dec. 28, 1993) (See 37 CFR 1.6(d)). NOTE: If applicants do submit a paper by fax, the original signed copy should be retained by applicants or applicants' representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
February 16, 1998

DAVID GUZO
PRIMARY EXAMINER
GROUP 1800